Remarks

Claims 11-13 were pending. By way of this response, the title has been amended to read more clearly, claims 11-13 have been cancelled without prejudice, and claims 14-24 have been added. Support for the new claims can be found in the application as originally filed, and no new matter has been added. Accordingly, claims 14-24 are currently pending.

Declaration

The Office Action requested a new oath or declaration because the declaration allegedly was defective for not identifying the mailing address of each inventor. As indicated in the Office Action, the mailing address may be provided in an application data sheet.

Enclosed is a copy of the declaration submitted for the above-identified continuation application in response to a Notice to File Missing Parts dated May 17, 2001. The declaration previously submitted identifies each of the four co-inventors, and immediately under the signature of each inventor, sets forth the inventor's complete residence address, including the zip code. In addition, the application data sheet submitted with the above-identified application on April 30, 2001 also correctly identified each inventor's mailing address.

In view of the above, applicant submits that the objection to the declaration is improper, and applicant requests withdrawal of the objection.

Res Judicata

Claims 11 and 12 have been rejected on the grounds of *res judicata*.

Claims 11 and 12 have been cancelled, and therefore the rejection is moot. Claims 14-24 have been added, and are directed to other embodiments for which patent protection is sought.

The legal doctrine of *res judicata* does not apply if either: (a) the claims of the above-identified application are patentably different from the claims that were previously adjudicated; or (b) the claims in the above-identified patent application involve a different issue as compared to the claims that were previously adjudicated. See e.g. MPEP § 706.03(w).

Applicant submits that the present claims, that is claims 14-24 are directed to different methods than the claims that were before the Board of Patent Appeals and Interferences in it's decision 1997-2367.

In view of the above, applicant submits that the doctrine of *res judicata* does not apply to the present claims, and applicant respectfully requests that this rejection be withdrawn.

Claim Objections

Claim 13 has been objected for recitation of "and B".

Claim 13 has been cancelled. Applicant submits that the objection is moot in view of the cancellation of claim 13.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claim 13 has been rejected under 35 U.S.C. § 112, first paragraph, as allegedly not being described in the specification in such a way as to convey that the inventors had possession of the claimed invention.

Claim 13 has been cancelled as set forth above.

Applicant traverses the rejection as it relates to the present claims. For example, the present claims recite methods that comprise a step of administering botulinum toxin type A to a subject followed by administration of botulinum toxin type E.

In view of the above, applicant submits that the present claims, that is claims 13-24, satisfy the requirements of 35 U.S.C. § 112, first paragraph, and respectfully requests that the rejection of the present claims based on this statutory provision be withdrawn.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 11 and 13 have been rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite.

Claims 11 and 13 have been cancelled, as set forth above.

Applicant traverses the rejection as it relates to the present claims. For example, the present claims do not include the phrase "substantially reduced response" or "and B", which served as the basis for rejection.

In view of the above, applicant submits that the claims satisfy the requirements of 35 U.S.C. § 112, second paragraph, and respectfully requests that the rejection of the present claims based on this statutory provision be withdrawn.

Rejections Under 35 U.S.C. § 103

Claims 11-13 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Ludlow et al. (hereinafter Ludlow) in view of Simpson et al. (hereinafter Simpson) and Jankovic et al. (hereinafter Jankovic).

Applicant does not concede with the rejections or remarks made in the Office Action. However, claims 11-13 have been cancelled as set forth above, and therefore, the rejections of the claims is moot. Applicant traverses the rejections as they relate to the present claims.

Applicant submits that the combination of Ludlow, Simpson, and Jankovic does not disclose, teach, or suggest the present invention. For example, the combination of Ludlow, Simpson, and Jankovic does not disclose, teach, or even suggest a method for treating a muscle spasm which comprises administering a therapeutically effective amount of botulinum toxin type A, and administering a therapeutically effective amount of botulinum toxin type E after the subject develops an immune response to

the administration of botulinum toxin type A, the immune response being selected from the group consisting of an allergic reaction, a delayed-type hypersensitivity, and a serum sickness-like response, or combinations thereof, as recited in claim 14. In addition, the combination of references does not disclose, teach, or even suggest a method of treating a patient having neuromuscular condition other than torticollis, oromandibular dystonia, or stuttering by administering a therapeutically effective amount of botulinum toxin type A to the patient, and administering a therapeutically effective amount of botulinum toxin type E to the patient after the patient exhibits a loss of clinical responsiveness to botulinum toxin type A, as recited in claim 19.

Ludlow specifically discloses administration of botulinum toxin type F to patient having either torticollis, oromandibular dystonia, or stuttering, and having antibodies to botulinum toxin type A. Claims 19-24 are directed to methods of treating patients that have a neuromuscular disorder or condition other than those disclosed by Ludlow. Claims 14-18 are directed to methods of treating humans who have an immune response to botulinum toxin type A, which immune response is not disclosed, taught, or even suggested by Ludlow.

The basis for the rejection under 35 U.S.C. § 103 is that it would be obvious to a person of ordinary skill in the art to substitute another botulinum toxin, such as botulinum toxin type E, for type F (as disclosed by Ludlow) because each of the botulinum toxins inhibit acetylcholine release.

Applicant disagrees, and submits that the remarks above are sufficient to distinguish the present claims from the combination of Ludlow, Simpson, and Jankovic. However, applicant also submits the following regarding significant differences between the various botulinum toxin serotypes, and regarding the patentability of the present claims.

Although it is known that the various serotypes are "antigenically distinct," applicant submits that it is unpredictable whether the administration of a second serotype toxin (for example type E) will provide a therapeutic effect after the first serotype (for example type A) has ceased to provide a therapeutic effect. In other words, the fact that the various serotypes are "antigenically distinct" does not mean that the antibody of one serotype does not cross-react with another type.

In fact, it was well known in the art at the time of filing of the above-identified application that antibodies to serotype botulinum toxin E bind to botulinum toxin serotypes B, C_1, and D (Tsuzunki et al., Infection and Immunity 56(4):898-902 (1988)); and antibodies to serotype toxin F bind to serotype botulinum toxin D (Ferreira, Applied and Environmental Microbiology 56(3):808 (1990)). (A copy of each of these articles is submitted herewith.) Furthermore, it was also well known that the ability of an antibody to bind to a toxin may block the effectiveness of the toxin to provide a therapeutic effect.

Accordingly, applicant submits that it is not obvious that an antigenically distinct toxin type E may be able to provide a therapeutic effect after the administration of type A ceases to

work, because antibodies to type A may cross-react with type E and block the therapeutic effectiveness of type E.

In addition, the various botulinum toxin serotypes differ in their protein size, degree of activation, and mechanism of action.

For example, botulinum toxin type E is produced in nonproteolytic bacterial strains (e.g., see Table 1 of the instant application). The presence of inactive botulinum toxin is believed to increase the antigenicity of the toxin. The presence of inactive botulinum toxin may also contribute to the differences in toxicities between type A and type E toxins.

Moreover, although all botulinum toxin serotypes inhibit acetylcholine release at the neuromuscular junction, they do so by affecting different neurosecretory proteins and/or cleaving the proteins at different sites. This is evidenced by, for example, Simpson et al., cited by the Examiner. For example, botulinum toxin types A and E both cleave the 25kD synaptosomal associated protein (SNAP-25), but they target different amino acid sequences within this protein. Botulinum toxin types B, D, and F act on vesicle-associated membrane protein (VAMP) with each serotype cleaving the protein at a different site. Botulinum toxin type C_1 has been shown to cleave both syntaxin and SNAP-25. These differences in mechanism of action may affect the relative potency and/or duration of action of the various botulinum toxin serotypes.

Furthermore, type A botulinum toxin is produced in both a 900kD and a 500kD form, types B and C_1 are produced as only a

500kD complex, type D is produced in both a 300kD form and a 500kD form, and types E and F are only produced in 300kD forms.

Despite the extensive research and extensive knowledge possessed by those working in this field, no one prior to the filing date of the above-identified application administered botulinum toxin type E to a patient after the patient lost clinical response to botulinum toxin type A in order to provide therapeutic relief.

In view of the above, applicant submits that the present claims, and claims independent 14 and 19 in particular, are unobvious from and patentable over Ludlow, Simpson, and Jankovic under 35 U.S.C. § 103.

In addition, each of the present dependent claims is separately patentable over the prior art. For example, none of the prior art disclose, teach, or even suggest the present methods including the additional feature or features, such as the dosages of botulinum toxin type A and botulinum toxin type E as recited in any of the present dependent claims. Therefore, applicant submits that each of the present claims is separately patentable over the prior art.

In conclusion, applicant has shown that the present specification is in proper form, and that the present claims are not subject to *res judicata*, satisfy the requirements of 35 U.S.C. § 112 and are not anticipated by and are unobvious from and patentable over the prior art under 35 U.S.C. §§ 102 and 103. Therefore, applicant submits that the present claims, that is claims 14-24 are allowable.

In view of the above, applicant respectfully requests the Examiner to pass the above-identified application to issuance at an early date. Should any matters remain unresolved, the Examiner is requested to call (collect) applicant's attorney at the telephone number given below.

Date: 9/28/04

Respectfully submitted,

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